10 / 550173 JC17 Rec'd PCT/PTO 21 SEP 2005

1 1. (Original) A process for the preparation of 2-(4-piperidinyl) methyl-1-indanone of

2 formula II, or a salt thereof,

$$R_2$$
 R_3
 R_4
 R_4
 R_4

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4 Formula II

- wherein R^1 , R^2 , R^3 , and R^4 are identical or different, and represent hydrogen, straight or
- 6 branched -chain alkyl, alkoxy, alkoxycarbonyl, alkyl- or dialkyl-aminocarbonyloxy,
- 7 trifluoromethyl, or halogen,
- 8 the process comprising reducing 2-(4-pyridyl) methyl-1-indanone of formula III, or a salt
- 9 thereof,

$$R_2$$
 R_3
 R_4
 R_4

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11 Formula III

- wherein R¹, R², R³, and R⁴ are as defined above; and recovering the 2-(4-piperidinyl) methyl-
- 13 1-indanone of formula II.
- 1 2. (Original) The process of claim 1, wherein R¹ and R⁴ represent hydrogen and R²
- 2 and R³ represent methoxy in formula II and formula III.
- 1 3. (Original) The process of claim 1, wherein the reduction comprises hydrogenation
- 2 in the presence of a catalyst.

- 1 4. (Original) The process of claim 3, wherein the catalyst comprises one or more of
- 2 platinum oxide, ruthenium oxide, and rhodium/carbon.
- 1 5. (Original) The process of claim 3, wherein the hydrogenation is carried out at a
- 2 pressure of from about 1 to about 2 atmospheres using hydrogen gas.
- 1 6. (Original) The process of claim 3, wherein the hydrogenation is carried out at a
- 2 temperature of from about 10°C to about 35°C.
- 1 7. (Original) The process of claim 3, wherein the hydrogenation is carried out in a
- 2 solvent.
- 1 8. (Original) The process of claim 7, wherein the solvent comprises one or more of
- ethers, alcohols, chlorinated hydrocarbons, esters, ketones, hydrocarbons, polar aprotic
- 3 solvents, water and mixtures thereof.
- 1 9.-15. (Cancelled).
- 2 16. (Original) The process of claim 1, wherein the recovering comprises one or more
- 3 of distillation, distillation under vacuum, filtration, filtration under vacuum, decantation, and
- 4 centrifugation.
- 1 17. (Original) A process for the preparation of 2-(4-pyridyl) methyl-1-indanone of
- 2 formula III, or a salt thereof,

$$R_2$$
 R_3
 R_4
 R_4

Formula III

- 5 wherein R¹, R², R³, and R⁴ are identical or different, and represent hydrogen, straight or
- 6 branched -chain alkyl, alkoxy, alkoxycarbonyl, alkyl- or dialkyl-aminocarbonyloxy,
- 7 trifluoromethyl, or halogen,

- 8 the process comprising selectively reducing 2-(4-pyridyl) methylene-1-indanone of formula
- 9 IV, or a salt thereof,

$$R_2$$
 R_3
 R_4
 R_4

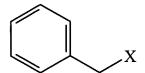
11 Formula IV

- wherein R¹, R², R³, and R⁴ are as defined above; and recovering the 2-(4-pyridyl) methyl-1-
- indanone of formula III.
- 1 18. (Original) The process of claim 17, wherein R¹ and R⁴ represent hydrogen and R²
- 2 and R³ represent methoxy in formula III and formula IV.
- 1 19. (Original) The process of claim 17, wherein the reduction comprises
- 2 hydrogenation in the presence of a catalyst.
- 1 20. (Original) The process of claim 17, wherein the catalyst comprises one or more of
- 2 palladium/carbon, platinum/carbon and Raney nickel.
- 1 21. (Original) The process of claim 17, wherein the hydrogenation is carried out at a
- 2 temperature of from about 10°C to about 35°C.
- 1 22. (Original) The process of claim 17, wherein the hydrogenation is carried out in a
- 2 solvent.
- 1 23. (Original) The process of claim 22, wherein the solvent comprises one or more of
- ethers, alcohols, chlorinated hydrocarbons, esters, ketones, hydrocarbons, polar aprotic
- 3 solvents, water, and mixtures thereof.
- 1 24.-30. (Cancelled).

- 1 31. (Original) The process of claim 17, wherein the recovering comprises one or more
- 2 of distillation, distillation under vacuum, filtration, filtration under vacuum, decantation, and
- 3 centrifugation.
- 1 32. (Original) A process for the preparation of benzyl-piperidylmethyl-indanones of
- 2 formula I, or a salt thereof,

$$R_2$$
 R_3
 R_4
 R_4

- 4 Formula I
- 5 wherein R¹, R², R³, and R⁴ are identical or different, and represent hydrogen, straight or
- 6 branched -chain alkyl, alkoxy, alkoxycarbonyl, alkyl- or dialkyl-aminocarbonyloxy,
- 7 trifluoromethyl, or halogen,
- 8 the process comprising reacting 2-(4-piperidinyl) methyl-1-indanone of the formula II, or a
- 9 salt thereof, prepared by the process of claim 1, with a benzyl derivative of formula V,



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- 11 Formula V
- wherein X is a leaving group; and recovering the benzyl-piperidylmethyl-indanones of
- 13 formula I.
- 1 33. (Original) The process of claim 32, wherein the leaving group X in the benzyl
- derivative of formula V is chloride, bromide, iodide, tosylate, or sulphate.
- 1 34. (Original) The process of claim 32, wherein the reaction is carried out in the
- 2 presence of a base and a phase transfer catalyst.

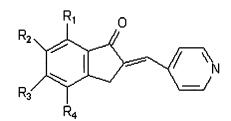
- 1 35. (Original) The process of claim 34, wherein the base comprises one or more of an
- 2 amine, an inorganic base and ammonia.
- 1 36. (Original) The process of claim 35, wherein the inorganic base is an alkali metal
- 2 carbonate.
- 1 37. (Original) The process of claim 36, wherein the alkali metal carbonate comprises
- 2 one or more of lithium carbonate, potassium carbonate and sodium carbonate.
- 1 38. (Original) The process of claim 34, wherein the phase transfer catalyst is
- 2 comprises one or more of quaternary ammonium salt, or quaternary phosphonium salt.
- 1 39. (Original) The process of claim 38, wherein the quaternary ammonium salt
- 2 comprises one or more of tetramethylammonium iodide, tetrabutylammonium iodide,
- 3 teramethyl-2-butylammonium chloride, trimethylcyclopropylammonium chloride,
- 4 tetrabutylammonium bromide, and t-butylethyldimethylammonium bromide.
- 1 40. (Original) The process of claim 32, wherein the reaction is carried out at a
- 2 temperature of from about 0°C to about 40°C.
- 1 41. (Original) The process of claim 32, wherein the reaction is carried out in a
- 2 solvent.
- 1 42. (Original) The process of claim 41, wherein the solvent comprises one or more of
- ethers, alcohols, chlorinated hydrocarbons, esters, ketones, hydrocarbons, polar aprotic
- 3 solvents, water and mixtures thereof.
- 1 43.-49. (Cancelled).
- 1 50. (Currently Amended) The process of claim 32, wherein the recovering
- 2 comprises one or more of distillation, distillation under vacuum, filtration, filtration under
- 3 vacuum, decantation, and centrifugation.
- 1 51. (Currently Amended) A process for the preparation of donepezil of formula VI
- 2 or a pharmaceutically acceptable salt thereof,

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Formula VI

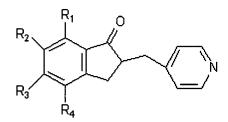
- 7 the process comprising:
- 8 (a) selectively reducing 2-(4-pyridyl) methylene-1-indanone of formula IV, or a salt thereof,



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to obtain 2-(4-pyridyl) methyl-1-indanone of formula III,



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- 13 Formula III
- wherein R¹ and R⁴ represent hydrogen and R² and R³ represent methoxy in formula III and
- 15 formula IV,
- 16 (b) reducing the 2-(4-pyridyl) methyl-1-indanone of formula III to obtain 2-(4-piperidinyl)
- 17 methyl-1-indanone of formula II,

$$R_2$$
 R_3
 R_4
 R_4
 R_4

19 Formula II

- wherein R¹ and R⁴ represent hydrogen and R² and R³ represent methoxy,
- 21 (c) reacting the 2-(4-piperidinyl) methyl-1-indanone of formula II,
- with a benzyl derivative of formula V,

$$\int$$

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24 Formula V

- wherein X is a leaving group, in the presence of an inorganic base and a phase transfer catalyst, and
- 27 (d) recovering the donepezil or a pharmaceutically acceptable salt thereof.
- 1 52. (Currently Amended) The process of claim 51, wherein the leaving group X in
- 2 the benzyl derivative of formula V is chloride, bromide, iodide, tosylate, or sulphate.
- 1 53. (Currently Amended) A pharmaceutical composition comprising a
- 2 therapeutically effective amount of donepezil or a pharmaceutically acceptable salt thereof
- 3 obtained by the process of claim 51; and one or more pharmaceutically acceptable carriers,
- 4 excipients or diluents.